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Efficacy of Cilostazol After Endovascular Therapy for Femoropopliteal Artery Disease in Patients With Intermittent Claudication

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Objectives The purpose of this study was to investigate whether cilostazol reduces restenosis and revascularization after endovascular therapy (EVT) for femoropopliteal lesions.

Background Cilostazol improves walking distance in patients with intermittent claudication and reduces restenosis after coronary intervention, but its efficacy remains unclear after EVT for femoropopliteal disease.

Methods This study was performed as a multicenter, randomized, open-label clinical trial. Eighty patients (mean age 70.7 ± 6.2 years, 84% men) with intermittent claudication due to a femoropopliteal lesion were randomly assigned to receive or not receive cilostazol in addition to aspirin. The primary end point was freedom from target vessel revascularization, and the secondary end points were the rate of restenosis and freedom from target lesion revascularization and major adverse cardiovascular events, defined as all-cause death, myocardial infarction, stroke, repeat revascularization, and leg amputation.

Results Clinical follow-up information was obtained in all patients. Patient, lesion, and procedural characteristics did not differ significantly between the 2 groups. Stenting was performed in 36 patients (cilostazol, 16; control, 20; $p = 0.36$). Freedom from target vessel revascularization at 2 years after EVT was significantly higher compared with the control group (84.6% vs. 62.2%, $p = 0.04$). The rate of restenosis was lower in the cilostazol group (43.6% vs. 70.3%, $p = 0.02$), and freedom from target lesion revascularization and major adverse cardiovascular events was higher in the cilostazol group (87.2% vs. 67.6%, $p = 0.046$, 76.8% vs. 45.6%, $p = 0.006$, respectively). There was no major bleeding in either group during follow-up period.

Conclusions Cilostazol reduced restenosis and repeat revascularization after EVT in patients with intermittent claudication due to femoropopliteal disease. (J Am Coll Cardiol 2009;53:48–53) © 2009 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) has a high prevalence worldwide. Furthermore, PAD damages the lower extremities and is complicated by ischemic disease in important organs, leading to a 5- or 6-fold increase in mortality due to coronary artery diseases and stroke in PAD patients (1).

Many PAD patients cannot undergo surgical revascularization and are often treated with endovascular therapy (EVT). The recently introduced nitinol stent has improved the patency rate for stenting of the femoropopliteal artery compared with conventional stents (2). However, the long-term patency rate of the nitinol stent is insufficient compared with bypass surgery, and many patients are still at high risk for restenosis and require adjuvant systemic therapy. The 2007 Trans-Atlantic Inter-Society Consensus II (TASC II) (3) recommended antiplatelet therapy as pharmacotherapy after percutaneous transluminal angioplasty and stent implantation. However, most evidence supporting perioperative antiplatelet therapy has emerged from studies on coronary artery disease, and little from EVT in PAD patients.

Cilostazol is an oral antiplatelet agent that is indicated for treatment of intermittent claudication (IC) (4), and in patients with coronary artery disease, cilostazol may lower restenosis and repeat revascularization after coronary intervention (5). Therefore, we conducted a multicenter trial to determine the efficacy of cilostazol in patients treated with EVT for femoropopliteal disease.

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Methods

Study design. The study was performed as a multicenter, randomized, open-label clinical trial. The effect of cilostazol in preventing restenosis and repeat revascularization after treatment of the femoropopliteal disease was evaluated for 24 months by comparison of cilostazol-treated patients and untreated patients. Patients with IC who had a de novo femoropopliteal disease without an inflow lesion, with an outflow artery, and with symptoms that were not improved by pharmacotherapy or exercise therapy were enrolled in the study before EVT. Other inclusion criteria were age ≥18 years and <80 years old, an ankle-brachial index of ≤0.9, and a percent diameter stenosis (%DS) of ≥50% by visual estimate on angiography. Patients with previous lower extremity bypass surgery, previous EVT in the femoropopliteal artery, acute onset limb ischemia, or severe lower extremity ischemic symptoms classified into Rutherford category 4, 5, or 6 were excluded.

Patient randomization and allocation to groups was performed using the envelope method by a researcher who was not involved in any other aspect of the study and who was blinded to the study procedure. The study was approved by the Institutional Review Board of each institution, and written informed consent was obtained from each subject. This study is registered with the University Hospital Medical Information Network–Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (no. UMIN000001434).

Study procedures. All patients were taking aspirin (81 to 100 mg/day) and ticlopidine (200 mg/day) and had been assigned to the cilostazol or noncilostazol (control) group by the day before EVT or earlier. Patients assigned to the cilostazol group received cilostazol (200 mg/day) for 2 consecutive years, with the initial administration of cilostazol on the morning of the day EVT was performed. Hemodialysis patients in the cilostazol group received the drug at a dose of 100 mg. For patients who were already taking cilostazol before EVT, oral treatment was suspended when informed consent was obtained, and they were assigned to a group. At the discretion of the surgeon, patients were treated with a commercially available balloon or a cutting balloon for stent implantation, and ticlopidine was stopped in these patients on or after the day of the procedure. Other patients who underwent stent implantation received oral ticlopidine for 4 weeks after the procedure.

Interventions. All procedures were performed using a 6- or 7-F sheath. Unfractionated heparin was injected intra-arterially before the intervention at a dose of 3,000 to 5,000 IU and added as required to maintain the active clotting time at ≥200 s. The target lesion was passed with a 0.018- or 0.014-inch guidewire, the diameter and length of the balloon or cutting balloon were determined by the surgeon on the basis of angiography, and the vessel was expanded. After balloon angioplasty for at least 60 s, angiography was conducted and stent implantation was then performed in patients who had a residual stenosis of >30% or a flow-limiting dissection. A commercially available self-expandable stent was used. The stent type was determined by the operators, and the stent size was chosen to be 1 to 2 mm larger than the vessel diameter determined.

Abbreviations and Acronyms

EVT = endovascular therapy
IC = intermittent claudication
MACE = major adverse cardiovascular events
MI = myocardial infarction
PAD = peripheral arterial disease
%DS = percent diameter stenosis
TLR = target lesion revascularization
TVR = target vessel revascularization

Follow-up. Patients were contacted 1 month after the procedure and asked to return for a clinic visit at 6, 12, and 24 months. At these times, evaluation of restenosis was performed using Duplex ultrasonography. Occurrences of bleeding, myocardial infarction (MI), stroke, repeat revascularization, and leg amputation were recorded.

Study end points. The primary end point was defined as the freedom from target vessel revascularization (TVR) at 2 years after treatment, and the secondary end points were binary restenosis rate and freedom from target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) after 2 years. MACE included death, nonfatal MI, stroke, percutaneous or surgical repeat revascularization, and leg amputation. Independent observers blinded to the medication evaluated the clinical follow-up data. Binary restenosis was defined as a peak systolic velocity ratio of ≥2.4 (6). No detectable signal was graded as complete occlusion.

Procedural success was defined as a residual stenosis of <30% and the absence of a flow-limiting dissection in angiography. Myocardial infarction was defined by a significant elevation of serum biomarkers (troponin above the MI level or creatinine kinase levels twice normal) or new Q waves on the electrocardiogram. Stroke was defined as cerebral stroke that persisted for at least 24 h and indicated the occurrence of a neurological deficit. Major bleeding was defined as a need for transfusion, surgical intervention, or hypotension requiring inotropic support. The target lesion was defined as the treated segment from 10 mm proximal to 10 mm distal. The target vessel was defined as the entire vessel of the treated limb. TLR was defined as any repeat EVT for restenosis or other complication of the target lesion with a %DS of ≥50% in angiography (core laboratory assessment). TVR was defined as any repeat revascularization by EVT or bypass surgery of any segment of the target vessel with a %DS of ≥50% in angiography.

Statistical analysis. Values are reported as mean ± SD. All analyses were based on an intention-to-treat principle. Continuous variables were examined by use of the unpaired *t* test or nonparametric analysis by the Mann-Whitney *U*

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test. Categorical variables were compared by the chi-square test. Time-dependent outcomes were analyzed by the Kaplan-Meier method and compared by log-rank test. A probability value of <0.05 was considered statistically significant.

Results

Baseline characteristics. Eighty patients were enrolled in the study between October 2004 and October 2005. Two patients met the exclusion criteria, and therefore 78 patients were assigned to the cilostazol (n = 39) and control (n = 39) groups (Fig. 1). Procedural success was obtained in 76 (97.4%) patients. Two unsuccessful patients in the control group required further medical therapy, and 1 showed worsening of symptoms and received cilostazol after post-operative day 43. The backgrounds of the patients (Table 1) and lesions (Table 2) did not differ significantly between the 2 groups. Stenting was performed in 36 patients (cilostazol group, 16; control group, 20; p = 0.36), and the use of various commercially available stents was similar between the 2 groups.

Compliance. Of 39 patients in the cilostazol group, 35 (89.7%) were taking cilostazol as directed. Two (5.1%) patients complained of palpitations, and oral administration was stopped on post-operative days 24 and 66, respectively. The other 2 patients had stopped or reduced the dose at their own discretion, and subsequently resumed taking the correct dose. Thirteen patients (cilostazol, 7; control, 6) underwent implantation of a drug-eluting stent for coronary artery disease and received ticlopidine continuously during the follow-up period. These patients who received triple antiplatelet therapy had no major bleeding complications over the observation period.

Clinical end points. Complete follow-up clinical data were obtained from all 78 patients. During the observation period, binary restenosis was found in 43 (55.1%) patients (cilostazol, 43.6% [17 of 39]; control, 70.3% [26 of 37]; p =

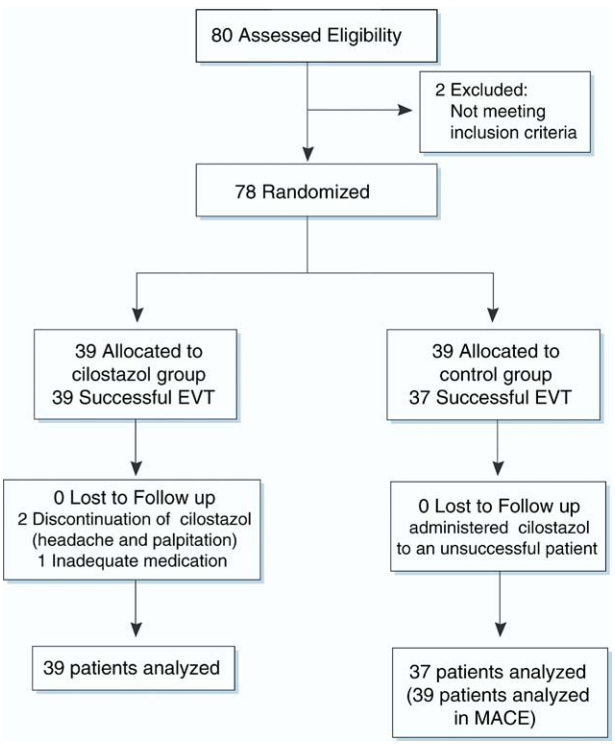

Figure 1 Participant Flow Through the Trial

EVT = endovascular therapy; MACE = major adverse cardiovascular events.

Table 1 Background of Patients Who Did and Did Not Receive Cilostazol

Variables	Cilostazol (+) (n = 39)	Cilostazol (−) (n = 39)	p Value
Age, yrs	69.8 ± 7.0	71.6 ± 8.1	0.30
Male (%)	31 (79)	34 (87)	0.36
Diabetes mellitus (%)	12 (31)	16 (41)	0.34
Hypertension (%)	19 (49)	19 (49)	0.99
Hypercholesterolemia (%)	15 (38)	11 (28)	0.34
Current smoker (%)	13 (33)	17 (44)	0.35
Renal failure (%)*	8 (21)	7 (18)	0.77
Coronary artery disease (%)	21 (54)	21 (54)	0.99
Previous MI (%)	5 (13)	10 (26)	0.15
Previous CABG (%)	3 (8)	5 (13)	0.46
Previous PCI (%)	16 (41)	17 (44)	0.82
Previous stroke (%)	9 (23)	8 (21)	0.78
Stent/CBA/BA	16/15/8	20/12/5	0.32
Use of stent (%)	16 (41)	20 (51)	0.36
Luminexx/SMART/Wall	5/8/3	6/13/1	0.39
Use of statin (%)	10 (26)	9 (23)	0.79
Use of beta-blocker (%)	7 (18)	4 (10)	0.33
Use of ACEI/ARB (%)	14 (36)	12 (31)	0.63
Pre-procedure ABI	0.59 ± 0.12	0.64 ± 0.15	0.13
Post-procedure ABI	0.81 ± 0.18	0.84 ± 0.16	0.49

*Renal failure defined as serum creatinine >1.5 mg/dl.

ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BA = balloon angioplasty; CABG = coronary artery bypass graft surgery; CBA = cutting balloon angioplasty; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2 Details of Lesions in Patients Who Did and Did Not Receive Cilostazol

Variables	Cilostazol (+) (n = 39)	Cilostazol (−) (n = 39)	p Value
Lesion length, mm	121.1 ± 67.3	131.5 ± 84.0	0.56
Pre-minimum lumen diameter, mm	0.92 ± 0.74	0.94 ± 0.81	0.31
Pre-diameter stenosis, %	78.7 ± 18.1	78.8 ± 18.2	0.99
Pre-reference diameter, mm	4.77 ± 0.72	4.85 ± 0.81	0.65
Post-minimum lumen diameter, mm	3.20 ± 0.98	3.27 ± 0.86	0.77
Post-diameter stenosis, %	28.0 ± 12.5	25.8 ± 12.1	0.46
Post-reference diameter, mm	4.78 ± 0.74	4.74 ± 0.91	0.85
TASC II, A/B/C/D	4/5/10/20	5/3/14/17	0.68
Chronic total occlusion (%)	10 (26)	14 (36)	0.33
Calcified lesion (%)*	8 (21)	6 (15)	0.56
Stent fracture at follow-up (%)	1 of 16 (6)	2 of 20 (10)	0.69

*Calcified lesion defined as obvious densities noted within the apparent vascular wall in the angiogram.

TASC II = Trans-Atlantic Inter-Society Consensus II.

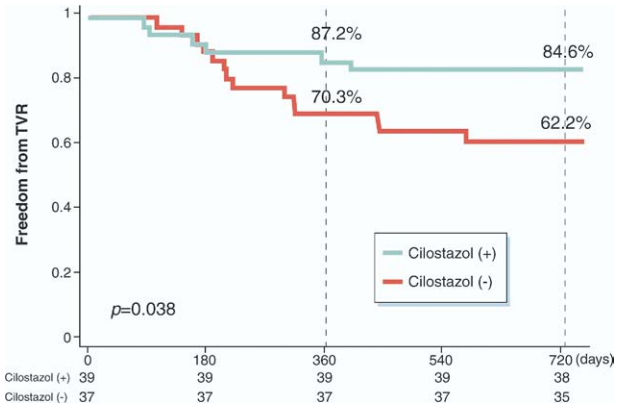

Figure 2 Freedom From TVR

Freedom from target vessel revascularization (TVR) after 24 months was significantly higher in the cilostazol (+) group **(green line)** compared with the cilostazol (−) control group **(red line)** (84.6% vs. 62.2%, p = 0.038).

0.02), and 8 had complete occlusion (cilostazol, 5.1% [2 of 39]; control, 16.2% [6 of 37]; p = 0.12). After 24 months, the freedom from TLR and TVR was significantly higher in the cilostazol group than in the control group (87.2% vs. 67.6%, p < 0.05; 84.6% vs. 62.2%, p = 0.04, respectively) (Fig. 2). The freedom from MACE was also significantly higher in the cilostazol group compared with the control group (79.5% vs. 48.7%, p = 0.006) (Fig. 3). There were no significant differences in death, MI, stroke, and leg amputation between the 2 groups; however, repeat revascularization was significantly lower in the cilostazol group than in the control group (18.0% [7 of 39] vs. 43.6% [17 of 39], p = 0.014) (Table 3). There were 3 deaths during the study: 1 in the cilostazol group (cardiac death) and 2 in the control group (1 cardiac and 1 noncardiac death). In 1 (2.6%)

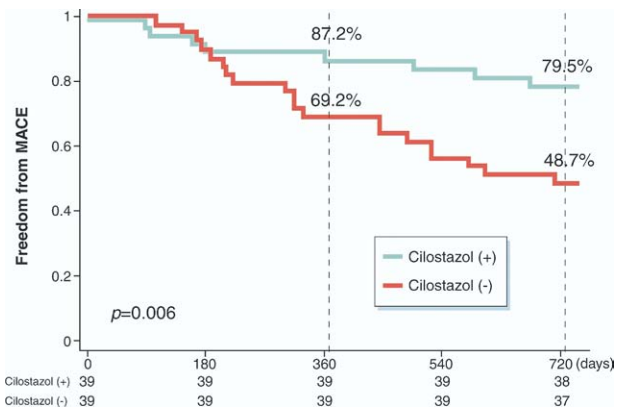

Figure 3 Freedom From MACE

Freedom from major adverse cardiovascular events (MACE) after 24 months was significantly higher in the cilostazol (+) group **(green line)** compared with the cilostazol (−) control group **(red line)** (79.5% vs. 48.7%, p = 0.006).

Table 3 Major Adverse Cardiovascular Events in Patients Who Did and Did Not Receive Cilostazol

	Total	Cilostazol (+) (n = 39)	Cilostazol (−) (n = 39)	p Value
Death (cardiac death)	3 (1)	1 (0)	2 (1)	0.60
Nonfatal MI	0	0	0	0.99
Stroke	1	0	1	0.31
Repeat revascularization	24	7	17	0.014
TLR	17	5	12	
TVR	20	6	14	
Non-TVR	5	2	3	
Surgical revascularization	1	1	0	
Leg amputation	0	0	0	0.99
Major bleeding	0	0	0	0.99

MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

patient in the control group, critical limb ischemia developed 16 months after the procedure. The resting ankle-brachial pressure index was significantly better at 24 months in the cilostazol group compared with the control group (0.81 vs. 0.72, p < 0.05) (Fig. 4).

Discussion

The effect of cilostazol after EVT for femoropopliteal disease was investigated in a multicenter randomized trial. Binary restenosis, TLR, and TVR after 2 years were significantly lower among patients treated with cilostazol compared with controls. We used provisional stenting to determine appropriate stent implantation on the basis of the results of balloon angioplasty. The rate of restenosis in the control group at 2 years after EVT was 70.3%. Schillinger et al. (7) reported a restenosis rate of 69.2% at 2 years after balloon angioplasty with optional secondary stenting (mean

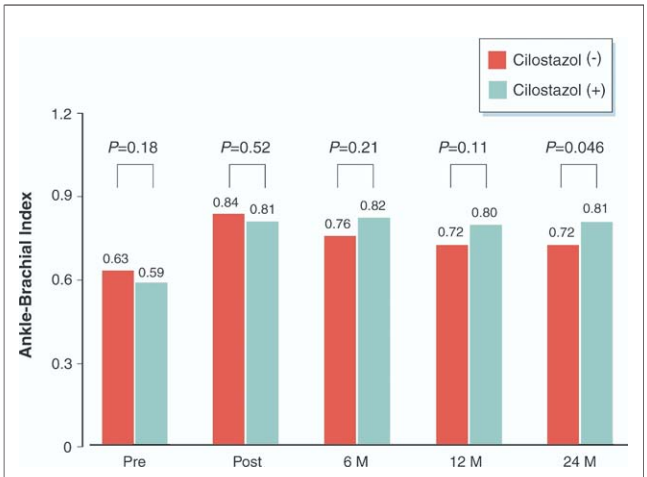

Figure 4 Resting Ankle-Brachial Pressure Index

The resting ankle-brachial pressure index was significantly better at 24 months in the cilostazol (+) group **(green bars)** compared with the cilostazol (−) control group **(red bars)** (0.81 vs. 0.72, p = 0.046).

lesion length, 93 mm), similar to the rate in this study. Iida et al. (8) reported that cilostazol administration after EVT to patients with femoropopliteal disease reduced restenosis and TLR. The TLR 2 years after EVT was 82% in the cilostazol group in this report, which is similar to the rate of 87% in the cilostazol group in our study. We note that the patients in the cilostazol group in the study by Iida et al. (8) had a longer lesion (mean lesion length, 141 mm) and more occlusive disease compared with our patients, and 29% had critical limb ischemia, which suggests that their lesion background was more severe.

The use and type of stent were determined by the operator, The nitinol stent is known to improve the long-term patency rate compared with conventional stents (2). However, stent fracture is an important factor in restenosis after stent implantation (9–11). Stent implantation was performed in 36 (46.2%) patients and a fracture was found in 3 (8.3%); however, these were only minor fractures and no restenosis occurred at the fracture site. A drug-eluting stent was implanted in native coronary artery in 14 (18%) patients who continued to receive ticlopidine at the discretion of the operator. Six of these patients also received cilostazol; therefore, they underwent triple antiplatelet therapy with aspirin, ticlopidine, and cilostazol. However, no major bleeding complications developed during the observation period. We note that cilostazol alone or in combination with other antiplatelet agents has previously been reported not to increase bleeding (12). In coronary artery disease, cilostazol reduces restenosis and repeat revascularization and appears to be safe, with no significant increase in the risk of bleeding, in a meta-analysis of randomized clinical trials comparing cilostazol with control therapy after coronary intervention (5). Our study gave a similar result for cilostazol administration in patients with femoropopliteal disease after EVT.

There are several possible reasons why oral administration of cilostazol reduced TVR. First, cilostazol is a stronger antiplatelet agent than aspirin, dipyridamole, and ticlopidine (13,14), and consequently, it has a more rapid effect (15). The TASC II guidelines (3) also recommend oral administration of antiplatelet agents to prevent early occlusion by thrombus at the treated site. A second reason is the reduction of restenosis caused by proliferation of neointima. Clinical study has shown cilostazol-associated suppression of neointimal hyperplasia (16). A third reason for the effect of cilostazol may be reduction in symptoms due to vasodilation induced by continuous relaxation of vascular smooth muscle. Several studies have reported that oral administration of cilostazol improves the walking distance and symptoms of PAD patients (17–20), and vasodilation may contribute to reduction of repeat revascularization.

A subgroup analysis was performed on patients with occlusive ($n = 24$) and nonocclusive ($n = 52$) diseases. Cilostazol administration reduced the rate of TVR in patients with nonocclusive disease (3.4% vs. 39%, $p = 0.001$), but not in patients with occlusive disease (50% vs. 36%, $p = 0.48$). The lesion length was longer (187 ± 73 mm vs. 98 ± 58 mm, $p < 0.0001$) and stent placement was more frequent (66.7% vs. 38.5%, $p = 0.02$) in patients with occlusive disease than it was in patients with nonocclusive disease. The higher rate of stenting in patients with occlusive disease was due to suboptimal results after balloon angioplasty; therefore, these patients are likely to have poorer characteristics. These subgroups were not established before the study, and the sample size was too small to evaluate whether the findings are due to a lack of treatment efficacy. The 24 patients with total occlusion were also classified into stent ($n = 16$; mean stent length, 165 ± 74 mm) and nonstent ($n = 8$) groups. The lesion length was longer in the stent group than in the nonstent group (207 ± 15 mm vs. 147 ± 80 mm, $p = 0.05$), but the rates of TLR (18.8% vs. 62.5%, $p = 0.03$) and TVR (25% vs. 75%, $p = 0.02$) and the reocclusion rate (12.5% vs. 50%, $p < 0.05$) were significantly lower in the stent group.

Study limitations. In interpreting our results, we note that the study has several limitations. First, it was designed to be a prospective randomized study, but was not double-blinded and only had a small sample size. Second, the clinical decision to perform TVR may have been biased, but to compensate for this limitation, TVR was performed after confirmation of ischemia-driven symptoms.

Conclusions

Long-term administration of antiplatelet agents is recommended for symptomatic PAD patients, but indications and appropriate agents have not been established. Therefore, the results of the current study are significant, because they show that a combination of cilostazol and aspirin reduces revascularization. Further studies involving PAD patients after EVT are required to establish the effect of treatment with cilostazol. However, the current results allow the conclusion that cilostazol reduces restenosis and repeat revascularization after EVT for femoropopliteal disease in claudicant patients.

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Key Words: femoropopliteal arterial disease ■ target vessel revascularization ■ restenosis ■ endovascular therapy.